A Liver Model for Chemoprotection against Malaria

PAGE meeting
13 June 2019
Stockholm

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MMV

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Medicines for Malaria Venture

We Can Do More!!!

At least 3 billion people at risk[1]

Estimated 435 000 deaths worldwide

61% deaths occur in children <5 years

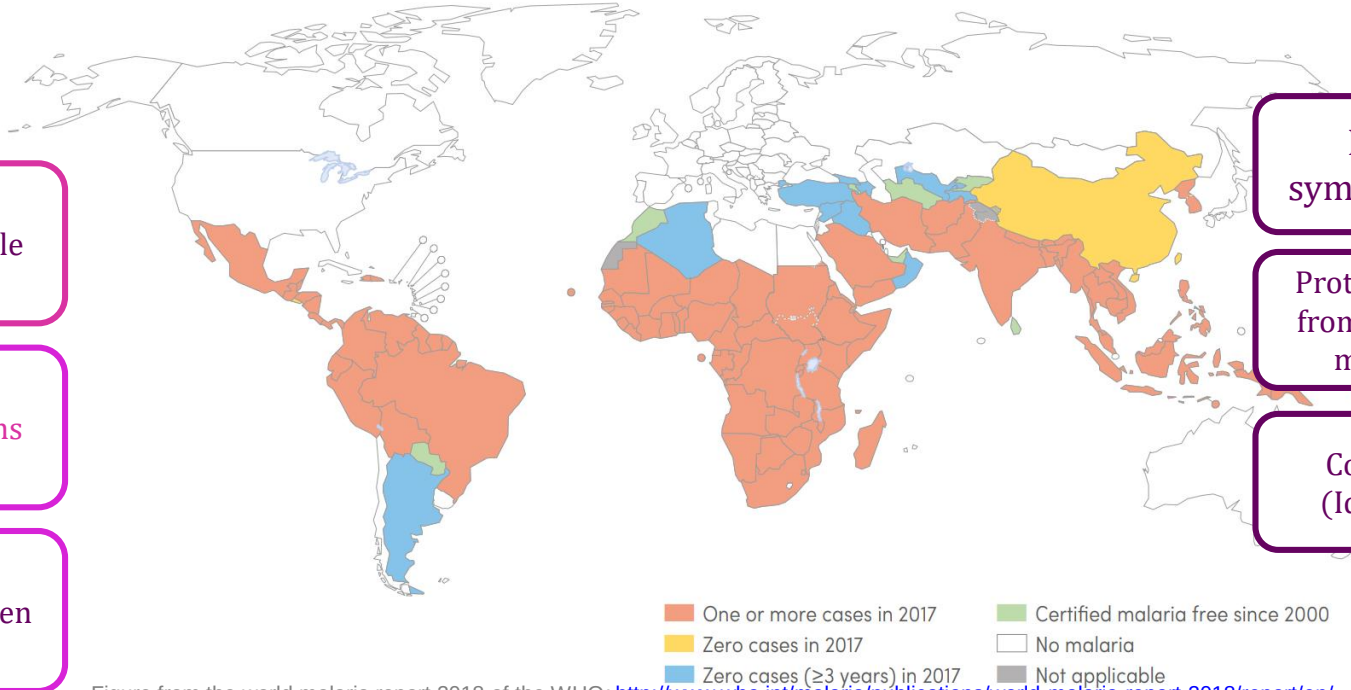

Figure from the world malaria report 2018 of the WHO: http://www.who.int/malaria/publications/world-malaria-report-2018/report/en/

Prevent acute symptomatic malaria

Protect Migrant Worker from low endemicity or malaria free areas

Cover for one week (Ideally one month)

Phillips, M. A. *et al.* (2017) Malaria
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2017.50

1. **WHO Malaria Fact Sheet, updated November 2018.**

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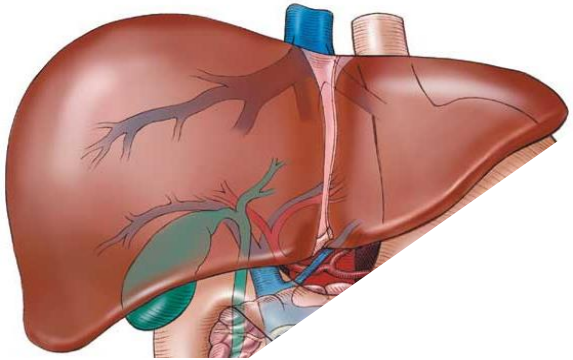
Parasite Life Cycle

HUMAN LIVER-STAGE

1 HOUR | 5–7 DAYS

HUMAN BLOOD STAGE

≥ 8 DAYS



Liver stage:

- Asymptomatic
- No Measurement

Blood stage:

- Symptomatic
- Blood Measurement

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Parasite Life Cycle

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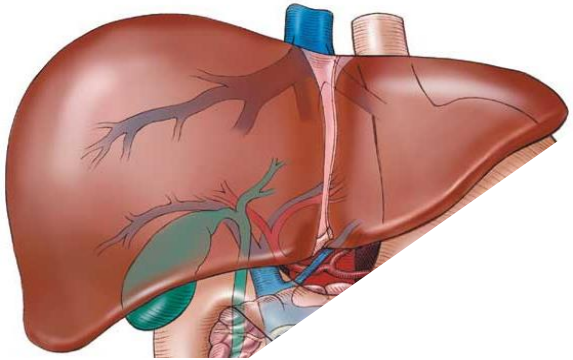

HUMAN BLOOD STAGE

≥ 8 DAYS

Liver stage:

- Asymptomatic
- No Measurement

Blood stage:

- Symptomatic
- Blood Measurement

Bottleneck and first stage of human infection
→ Attractive target for prophylaxis

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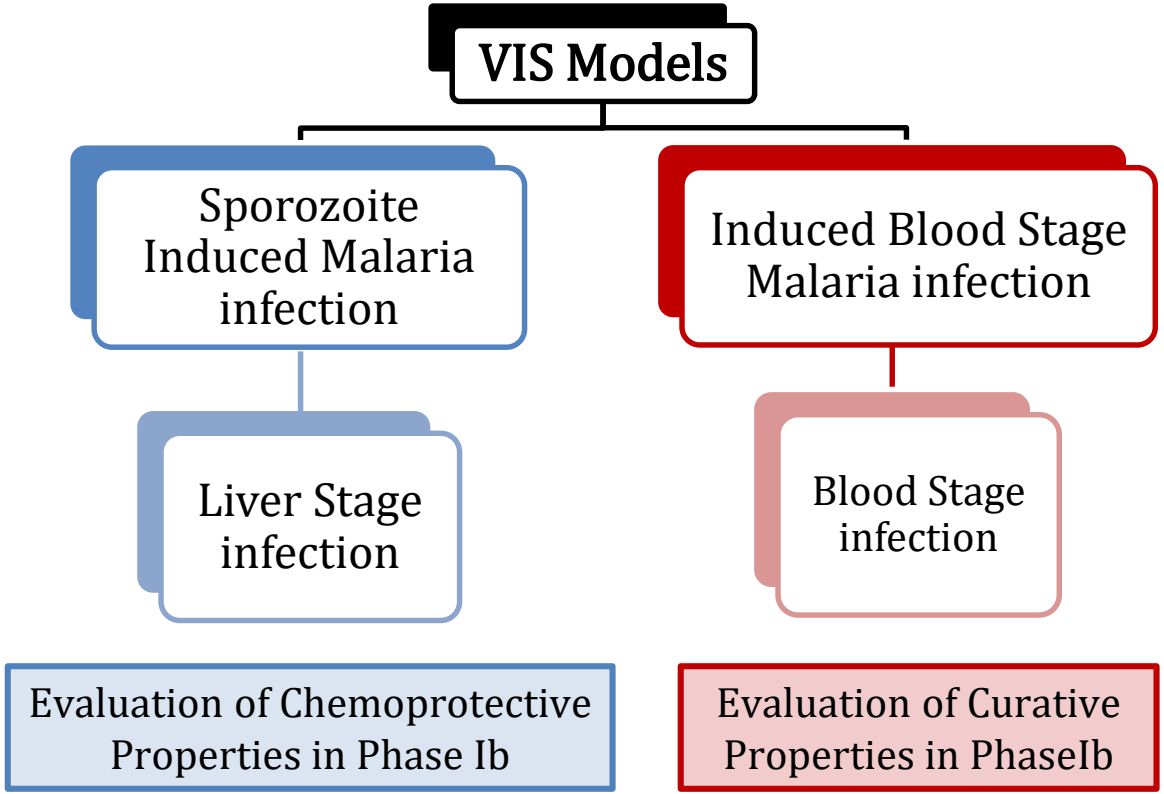
Objective

Can a PKPD model for liver stage be developed to support clinical study design & dose selection for Phase II?

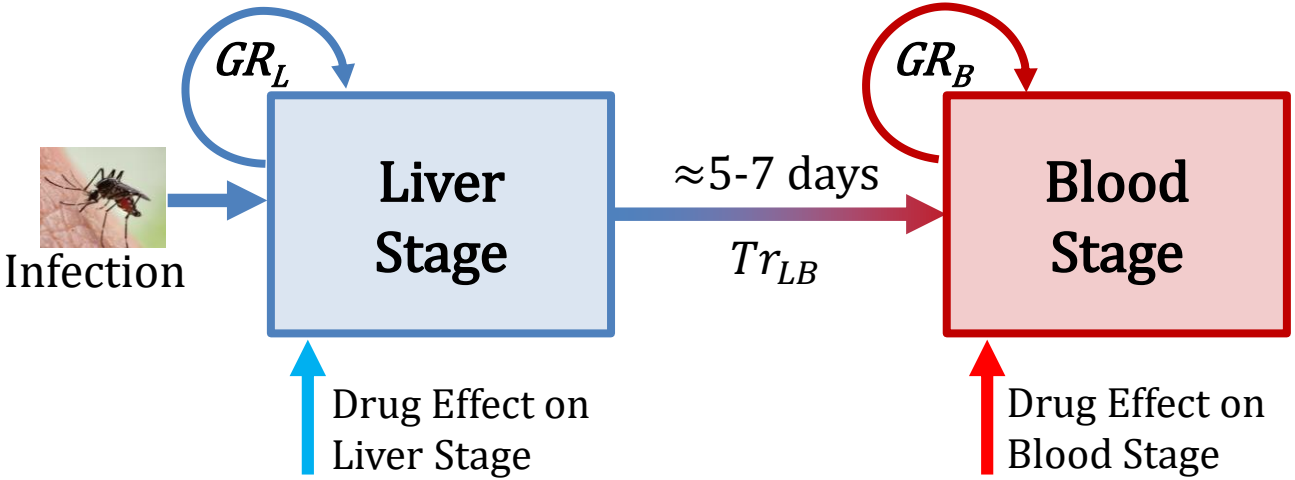
Volunteer Infection Study (VIS) Models



Type of Data

	LIVER STAGE	BLOOD STAGE
Study	Volunteer Infection Study (VIS)	
Route of Infection	IV inoculation of Sporozoites (Parasite Form in Mosquito Salavia)	IV inoculation of Infected Red Blood Cells (iRBC)
Parasite Dynamic	Not Measurable in Human	Directly Measurable (Blood Sampling)
Drug Activity	Indirect Observation via Blood Stage	Directly Measurable (Blood Sampling)

Model Overview



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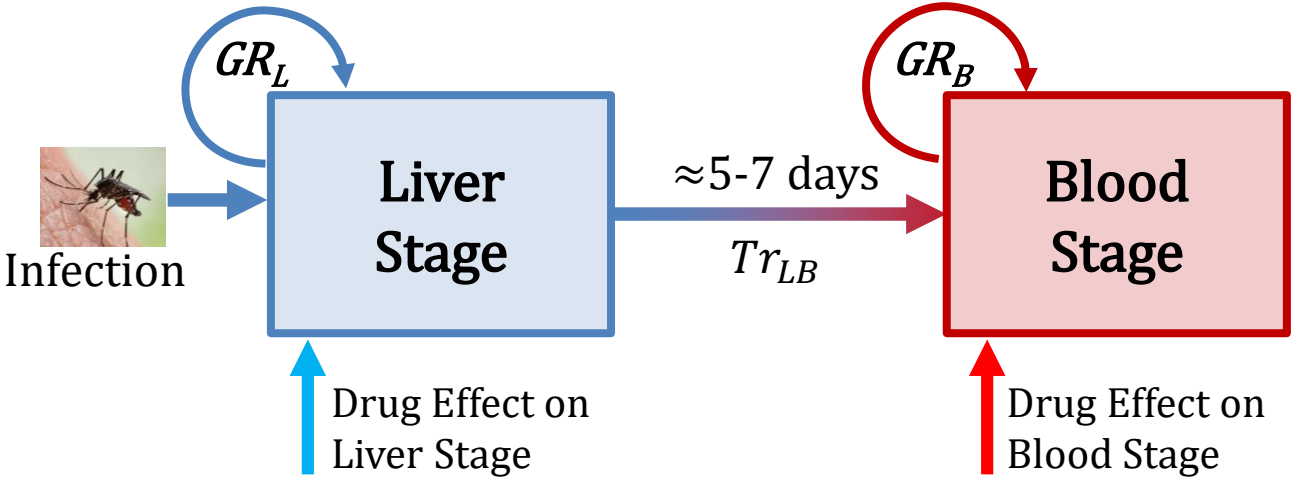


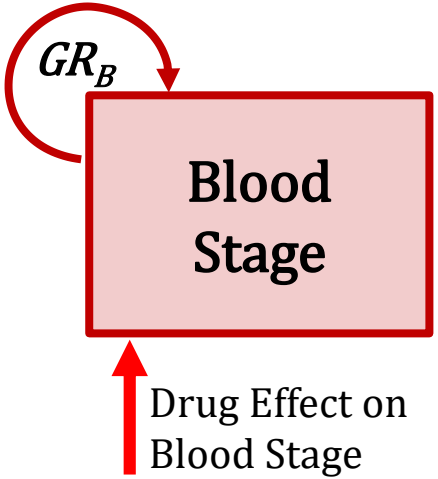
$$\frac{dP_L}{dt} = P_L * (GR_L - Kill_L(C)) - Tr_{LB}$$

$$\frac{dP_B}{dt} = P_B * (GR_B - Kill_B(C)) + Tr_{LB}$$

with $$Tr_{LB}(t) = k_{LB} P_L \frac{1}{1 + e^{-\frac{t-6\text{day}}{\sigma_t}}} \approx \begin{cases} 0 & \text{for } t < 6\text{d} \\ k_{LB} P_L & \text{for } t > 6\text{d} \end{cases}$$

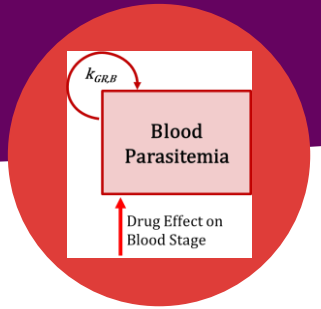
& $$P_L(t = 0) = ???$$

Blood Stage

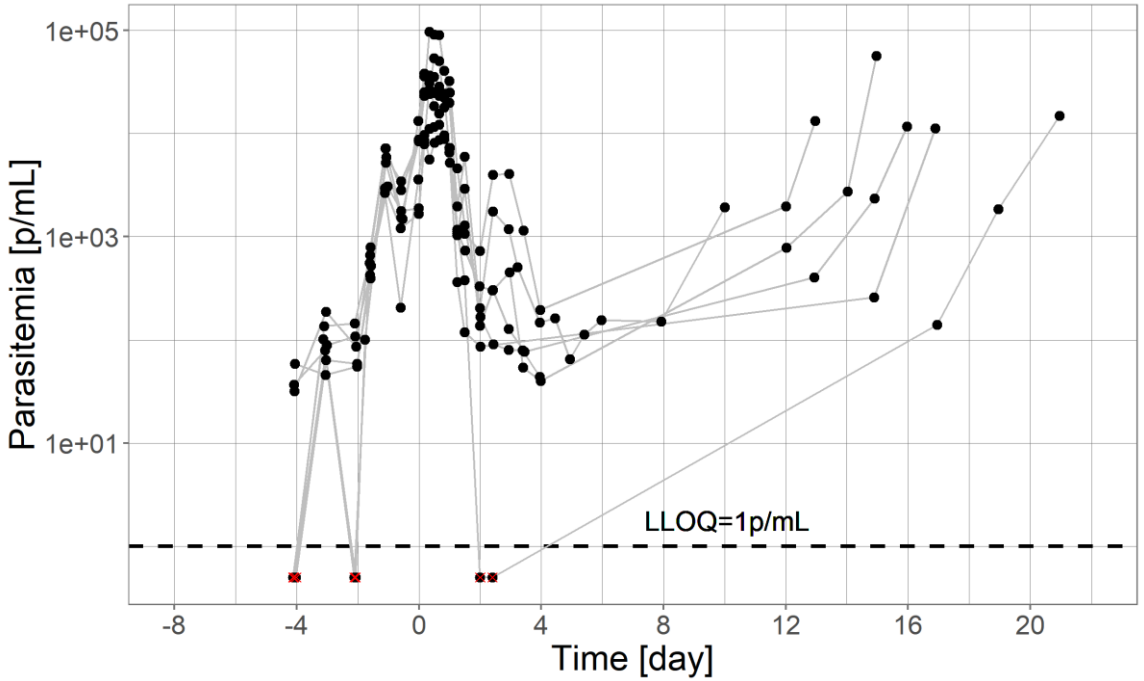


$$\frac{dP_B}{dt} = P_B * (GR_B - Kill_B(C))$$

Clinical Data



- Infected RBC (iRBC) are injected to volunteers.
- Parasite growth in the blood for 7/8 days prior treatment with DSM265.
- Clearance of the parasite, potentially followed by a recrudescence.



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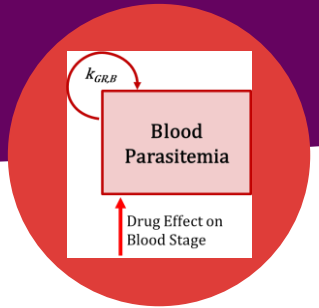

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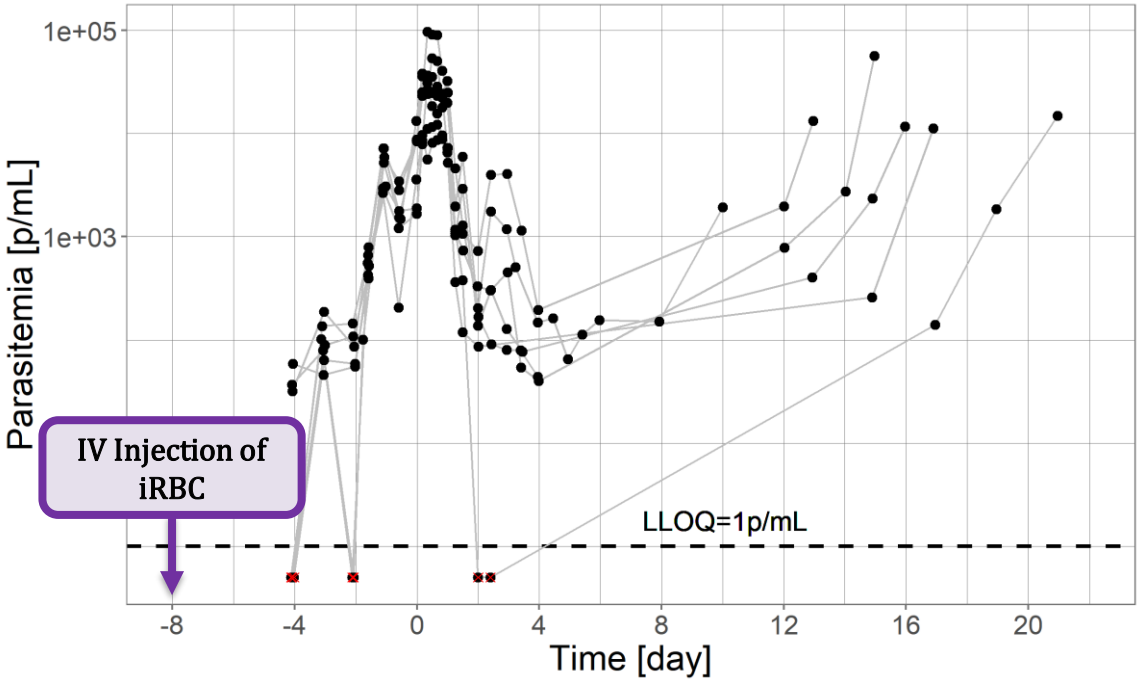

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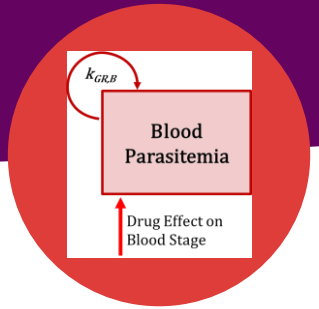

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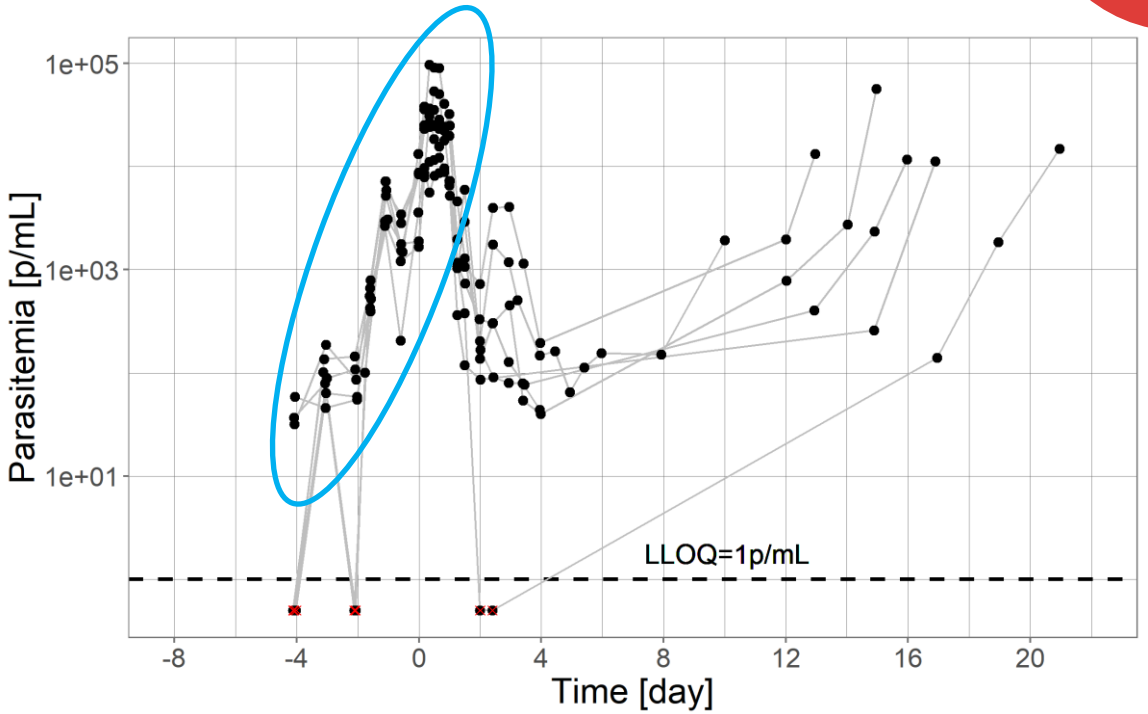

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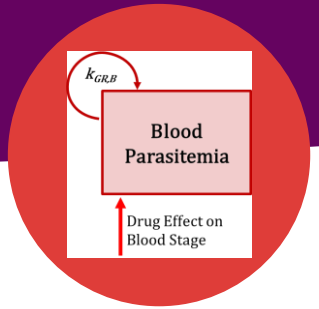

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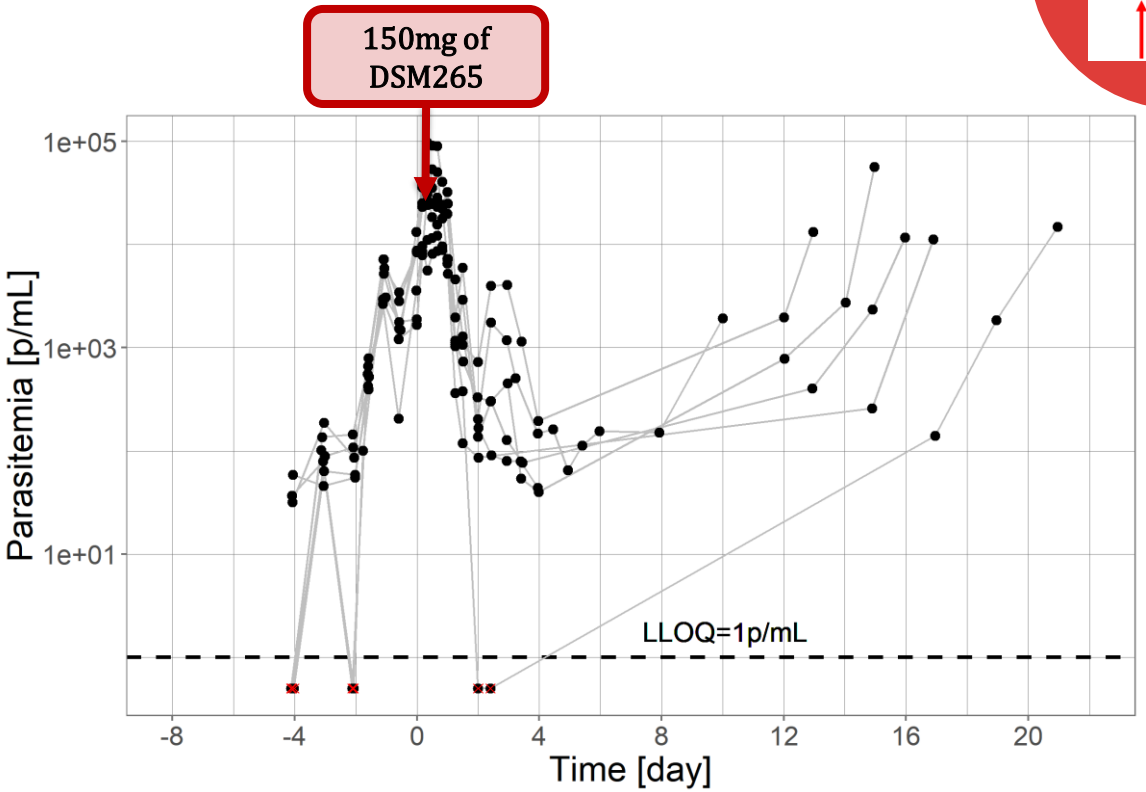

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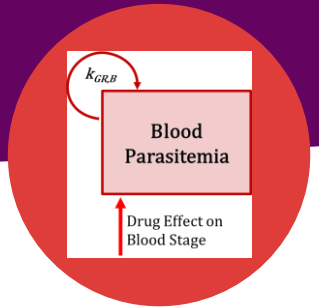

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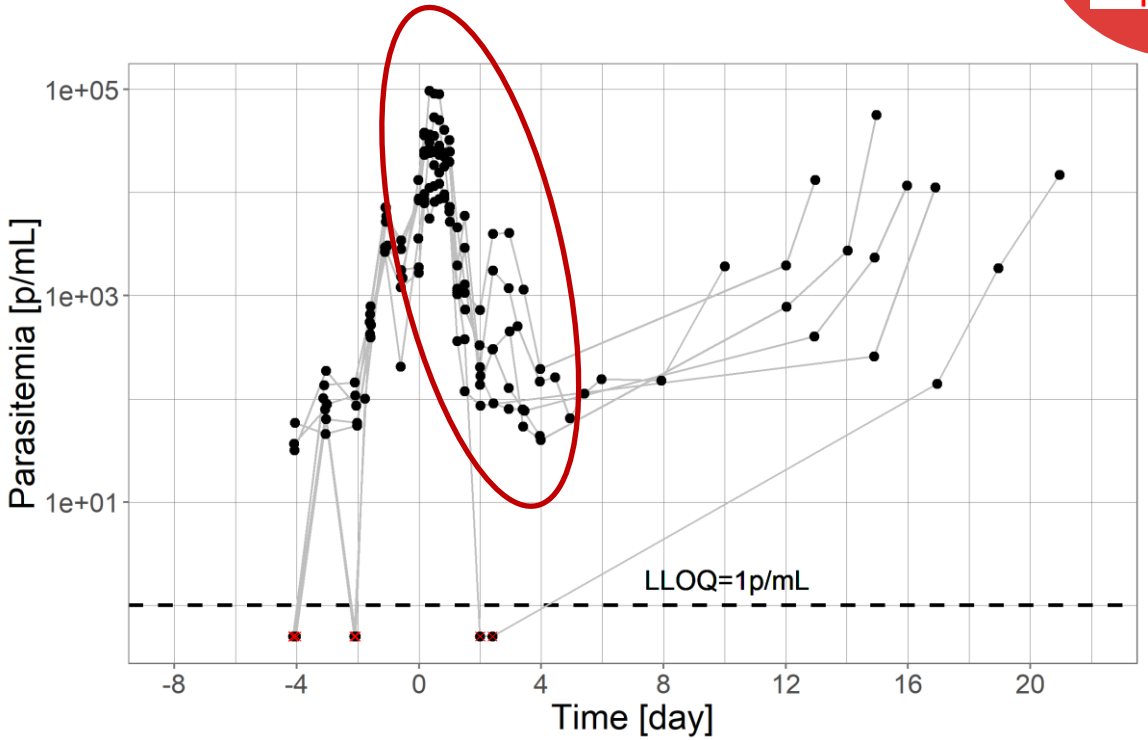

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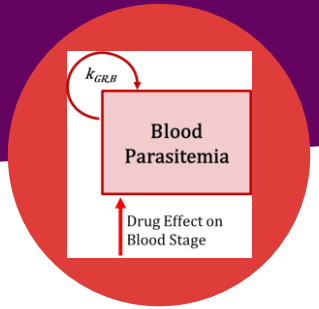

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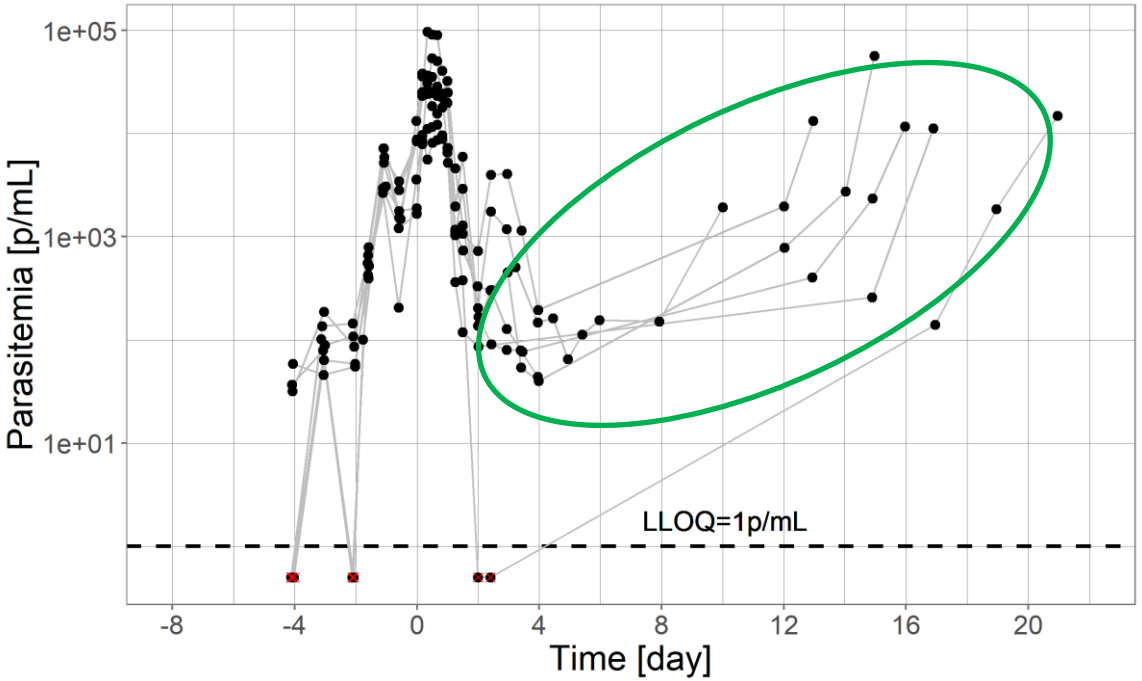

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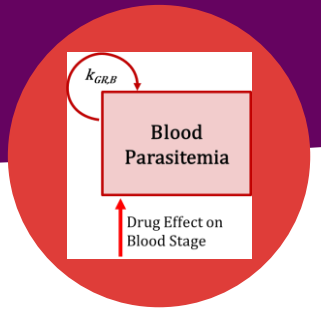
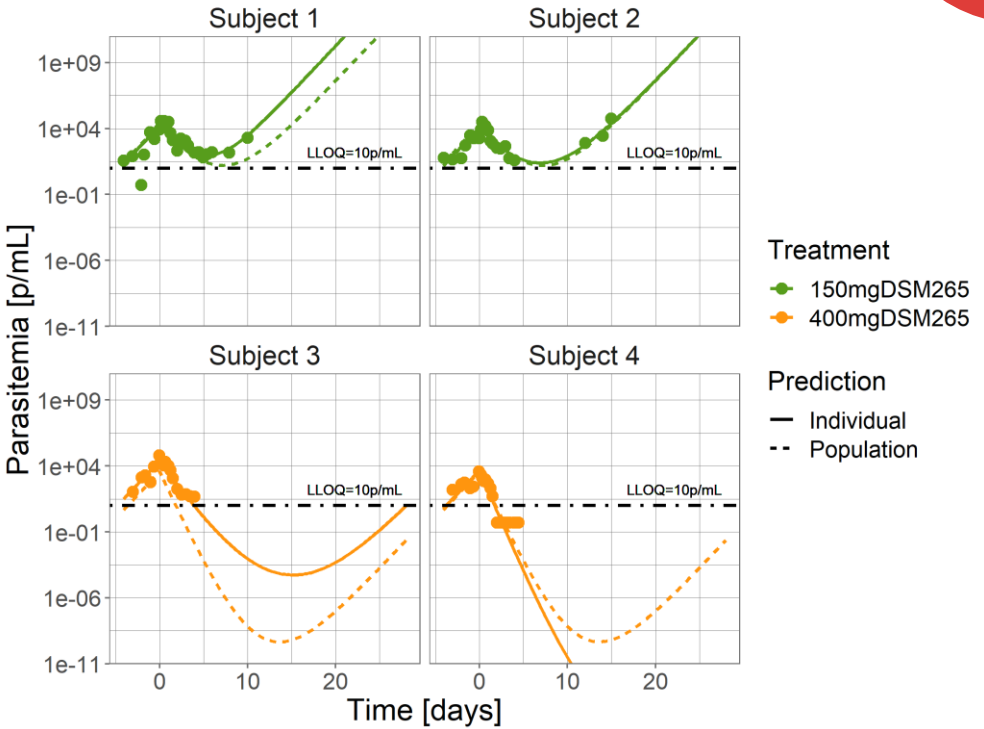
PKPD modelling



- All PD parameters can be identified.
- *e.g.* E_{max}-model:

$$Kill = \frac{E_{max} C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$



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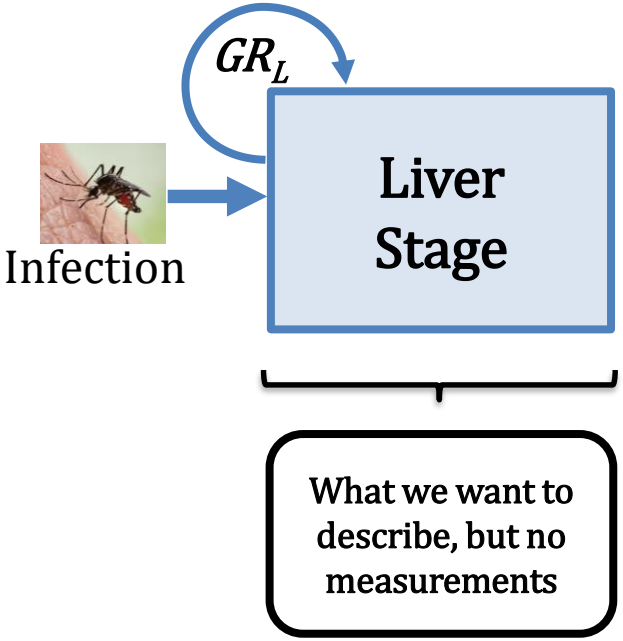
Parasite Growth in Liver Stage?



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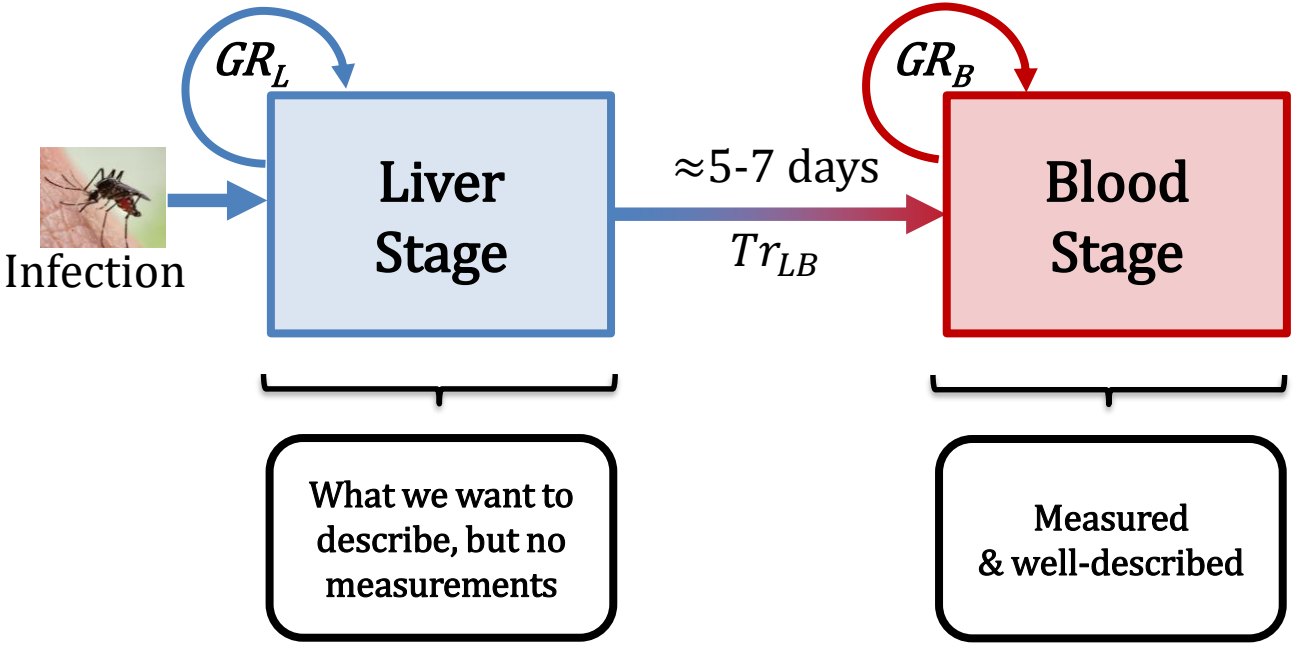
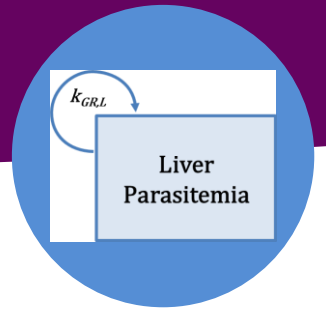
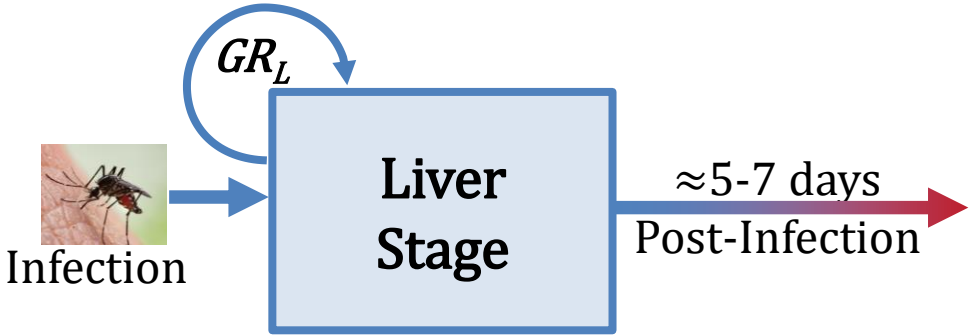


What is known?





1. Each invaded hepatocytes releases 10,000 to 50,000 parasites into the blood.

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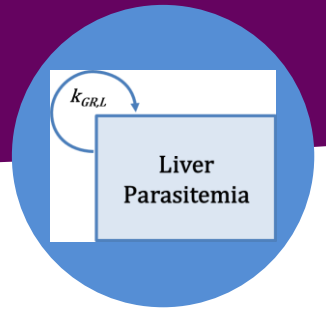

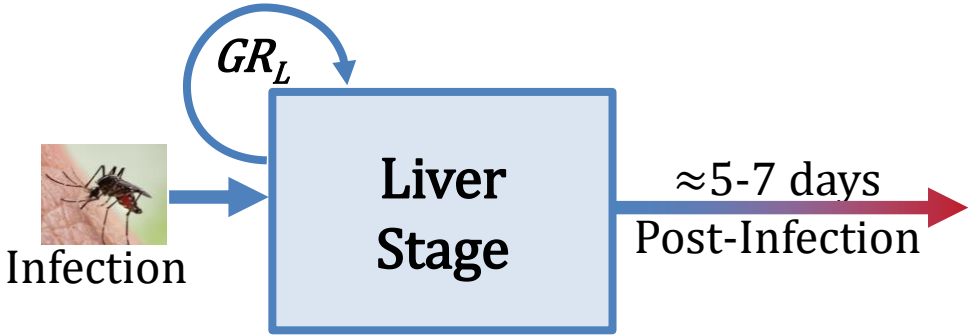

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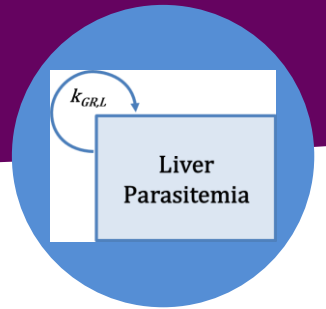

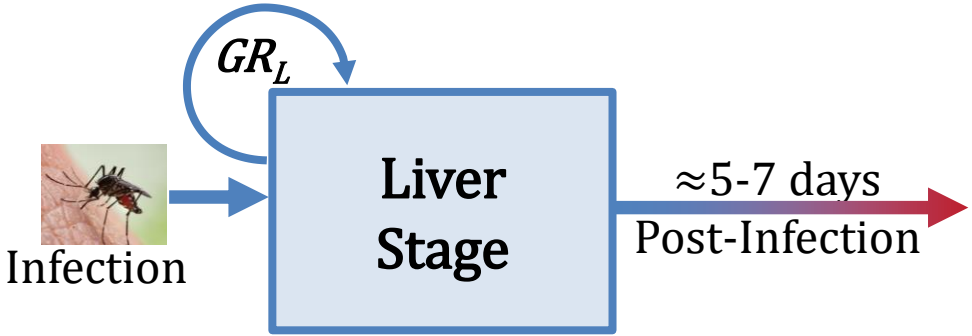

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Assuming exponential growth:

$GR_L \approx 0.072\ hr^{-1}$

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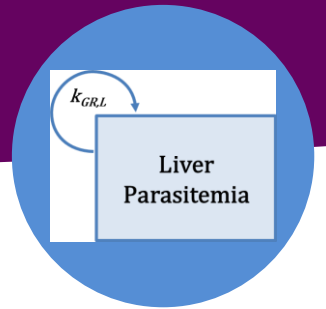

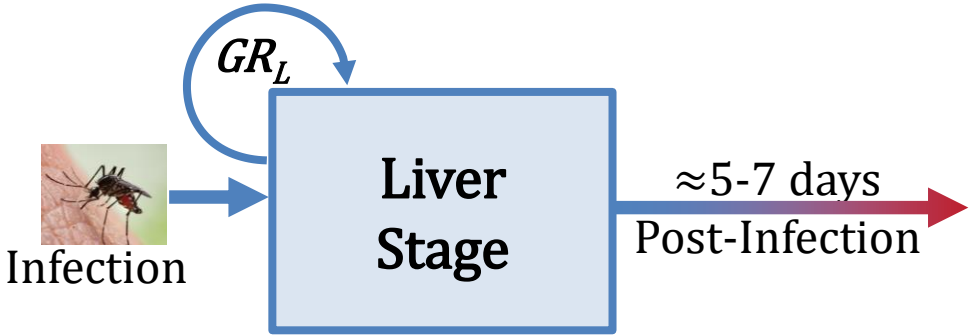

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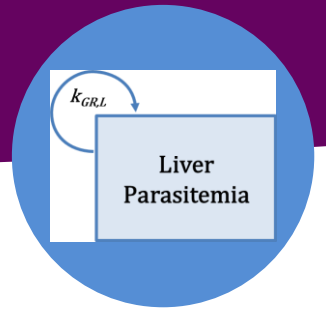

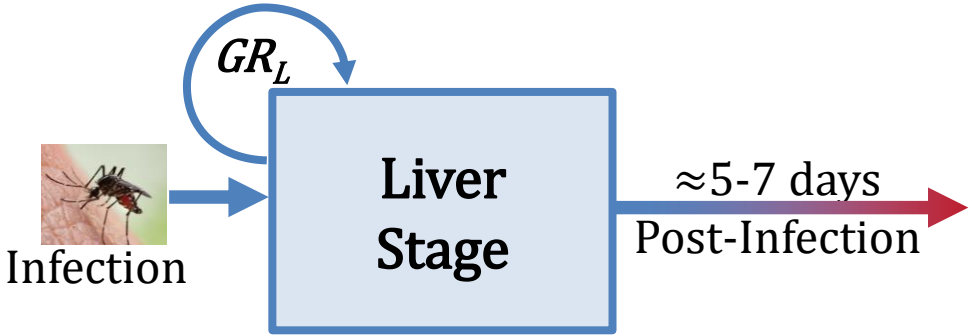

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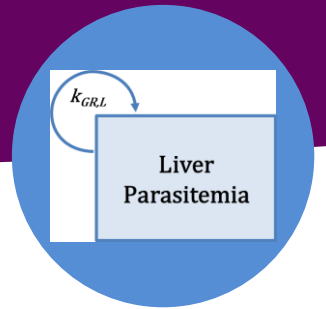

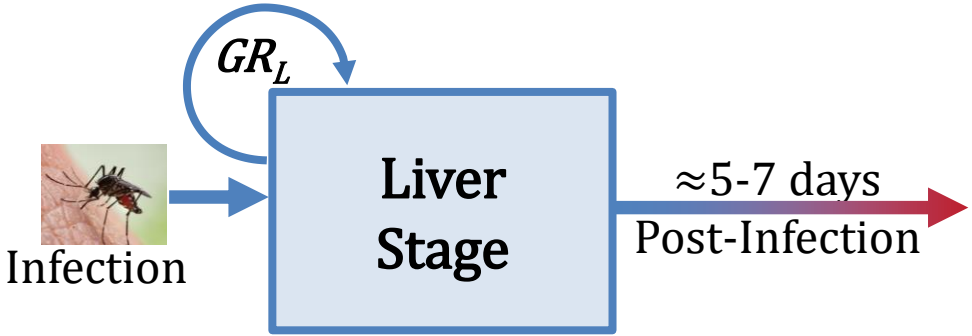

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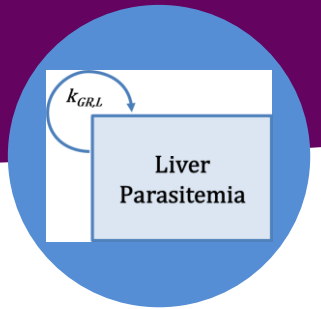
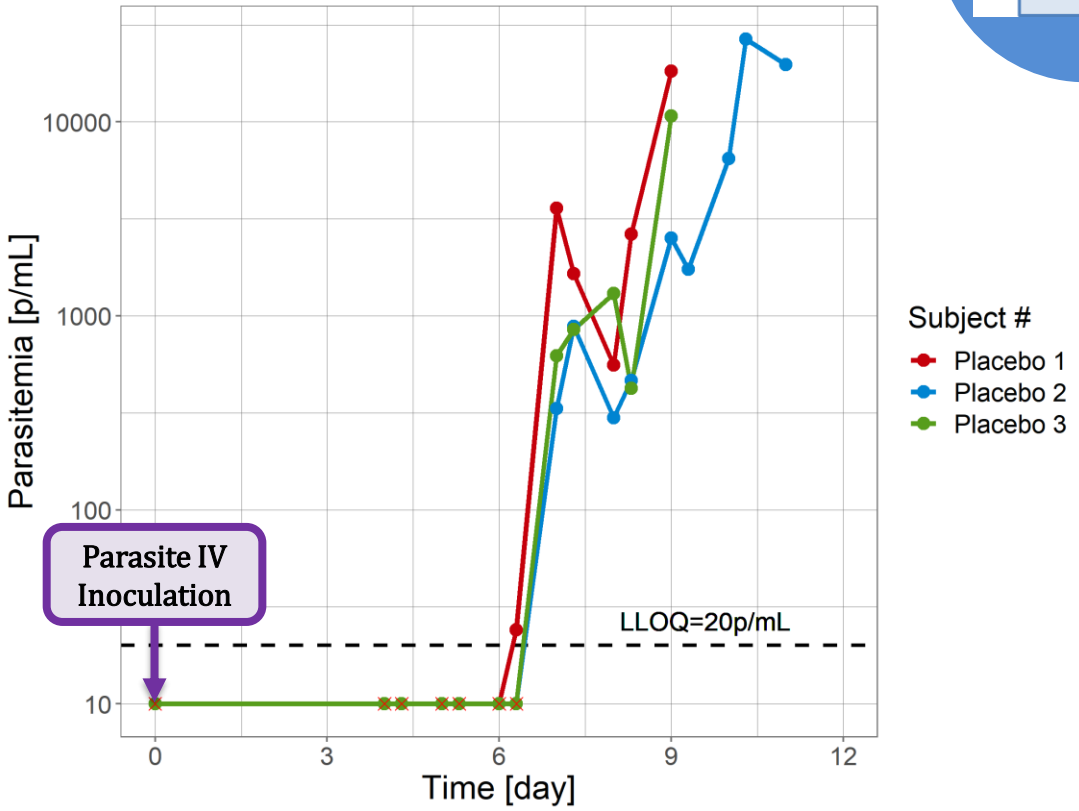
Parameter to be estimated:
Infected Fraction F_{inf}

Clinical Data



- Volunteers are inoculated with 3,200 parasites.
- First appearance of parasite in blood after day 6 post-inoculation



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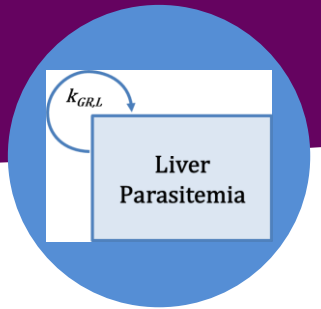
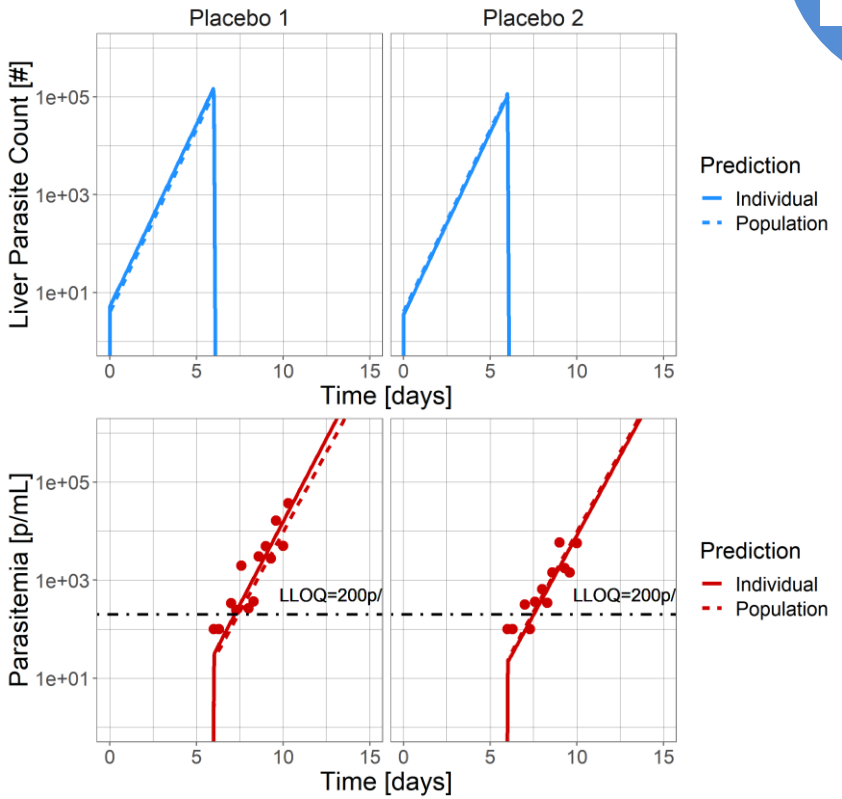
Initial Parasitemia Identifiability



- From the model, estimation of $F_{inf} \sim 0.12\%$.
- Which corresponds to ~4 infected hepatocytes.



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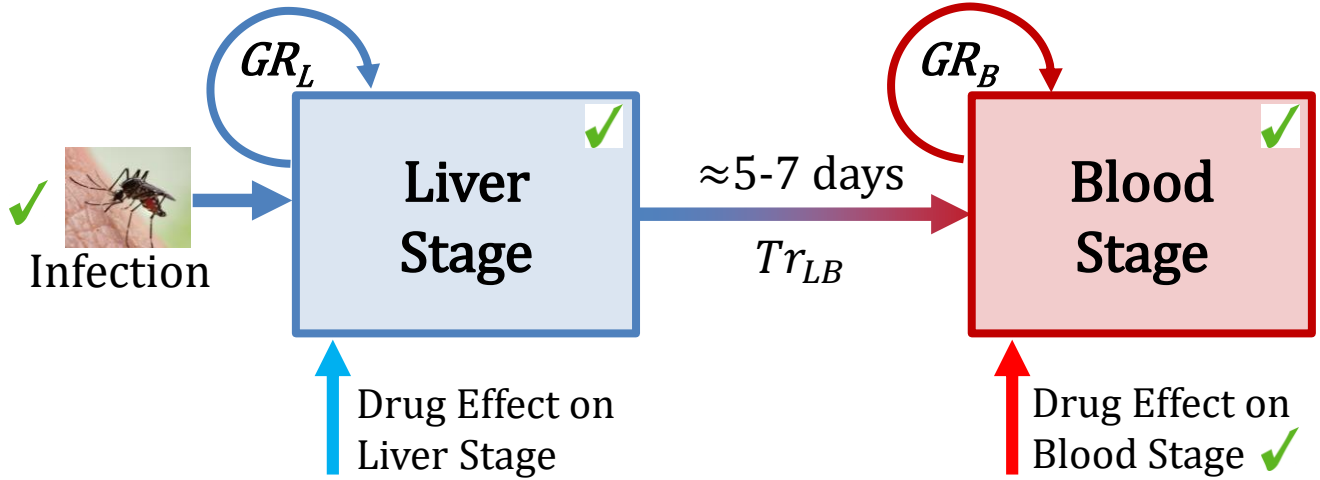
Drug Activity in Liver Stage?



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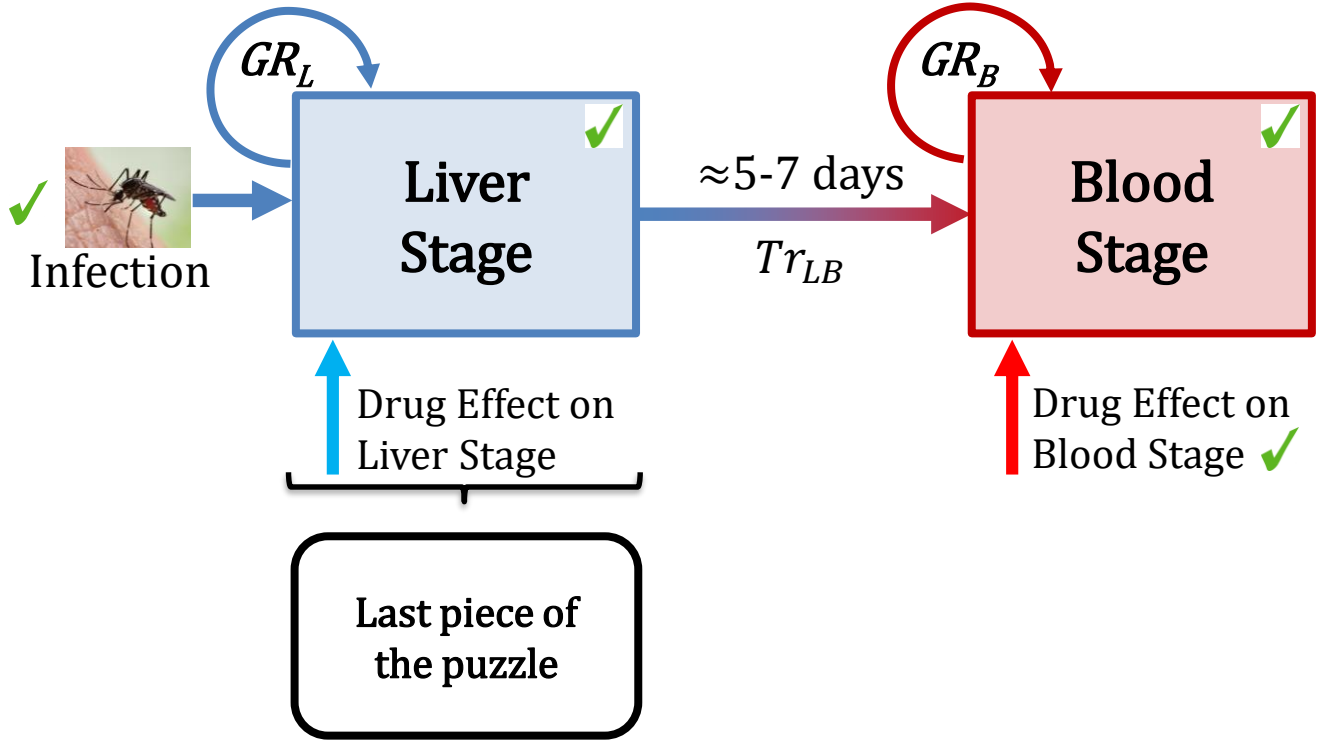
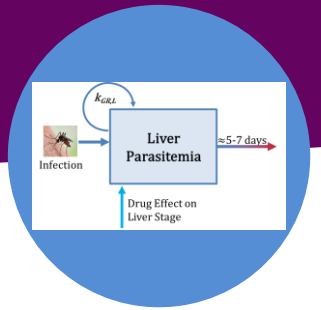
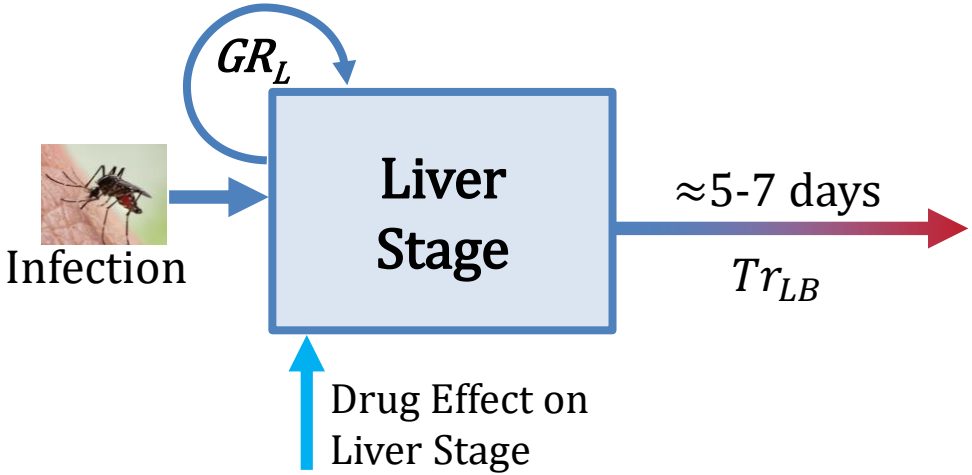


Drug Activity Assumptions

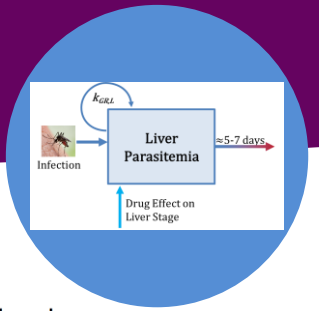




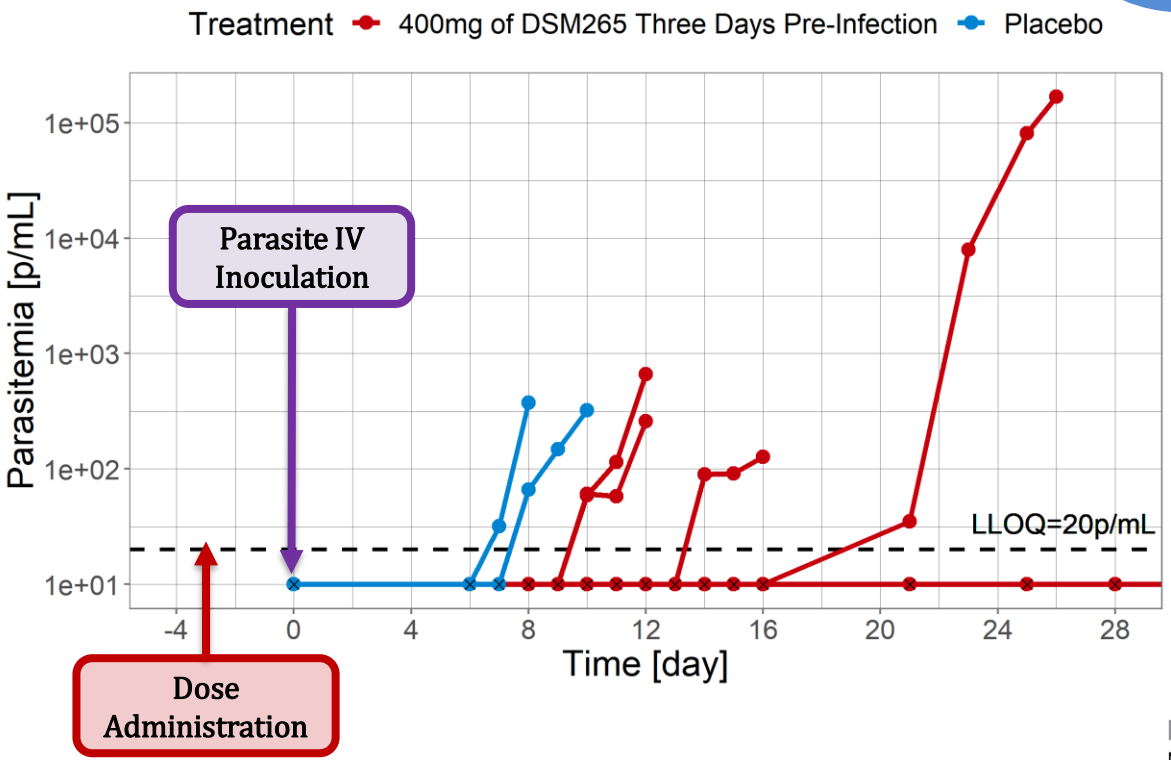
1. DSM265 does not affect the duration of the liver stage.

2. DSM265 has identical mode of action in blood and in liver stage.
   ⇒ E_{max} and *hill* coefficients are assumed to be equal between the two stages

Clinical Data



- Two Placebo
- Six volunteers were administered 400mg DSM265 three days prior **infection**.



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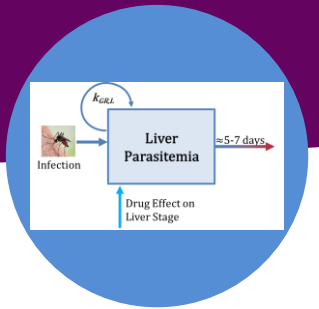
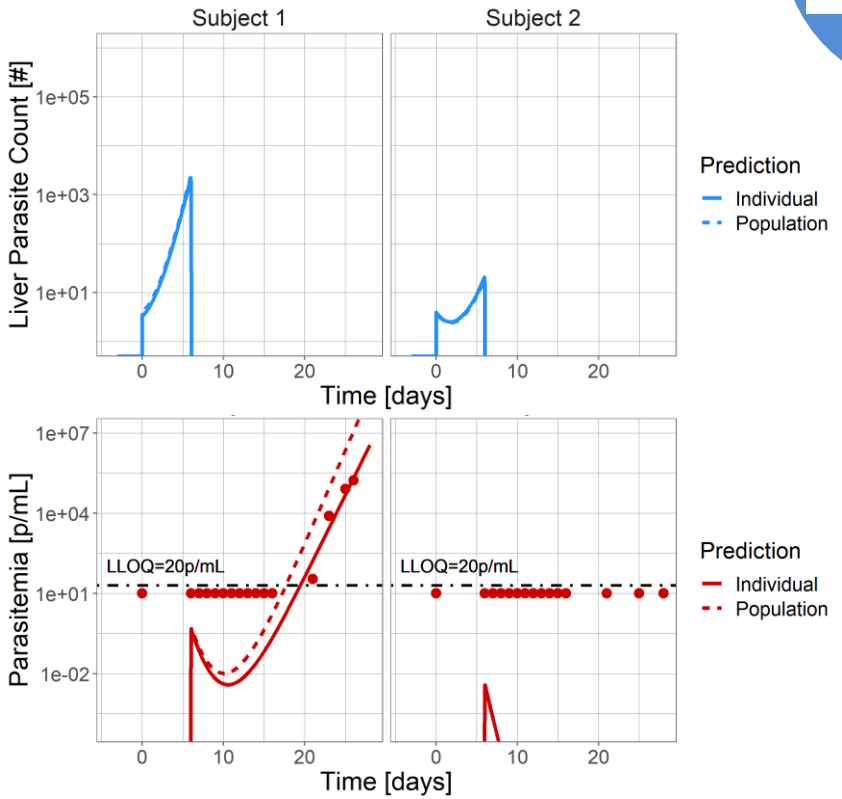
PD Parameters Identifiable



- $EC_{50,L}$ estimated to be 6540ng/mL ($EC_{50,B}$=830ng/mL)



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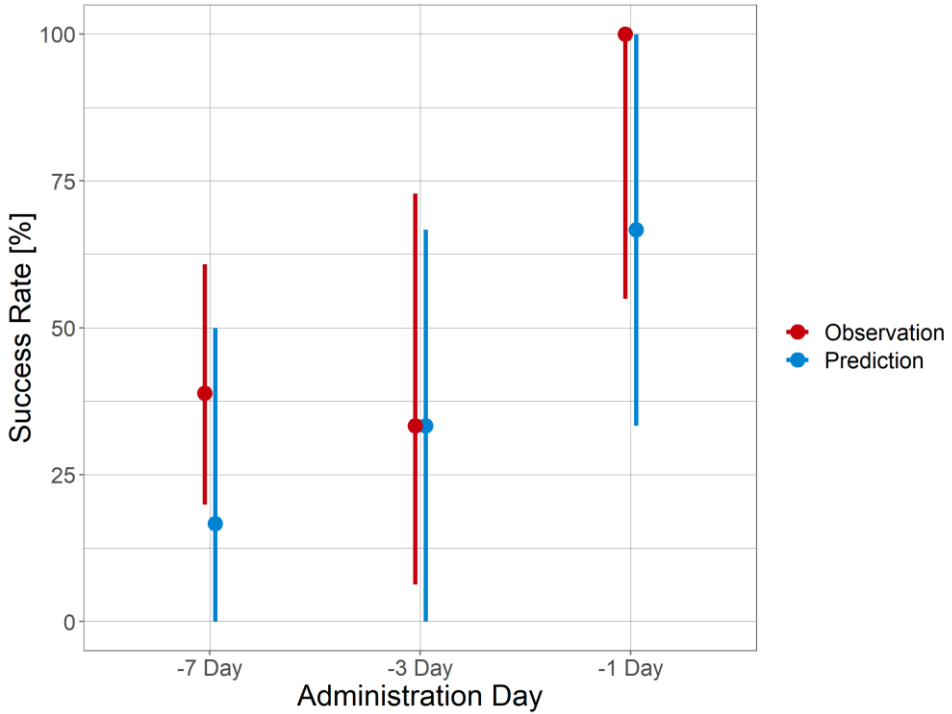
Model Validation

- **Model-based prediction of success rate compared to observation**
  Percentage of patients malaria-free at Day 28



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Conclusion

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Conclusion

- **Focus was to work on each stage of the life cycle:**
  - ⇒ The blood stage is well characterize (growth and drug activity).
  - ⇒ Understanding the liver dynamic is key (required assumptions)
- **A PKPD model was able to be derived:**
  - ⇒ Despite the lack of direct measurements at liver stage
- **Can support dose selection for chemoprotection.**

Perspectives:

- Sensitivity analysis on the assumptions
- Simulation accounting for adherence
- Different transfer function (*e.g.* transfer more distributed over time)
- Integrate knowledge from future *in vivo* studies

Acknowledgements

MMV Colleague:

Nicole Andenmatten, Aline Fuchs, Nathalie Gobeau, Jörg Möhrle

UK-QSP Team:

Chiara Fornari (AstraZeneca), Prof. John Ward (Uni. of Loughborough), Lydia Burgert (Uni. of Basel), Michael Gabel (Uni. of Heidelberf), Nicole Andenmatten (MMV), Oluwaseun F. Egbelowo (Uni. of Witwatersrand), Rolf Fendel (Uni. of Tübingen)

Our funding partners without whom we couldn't do any of this work

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Back-Up

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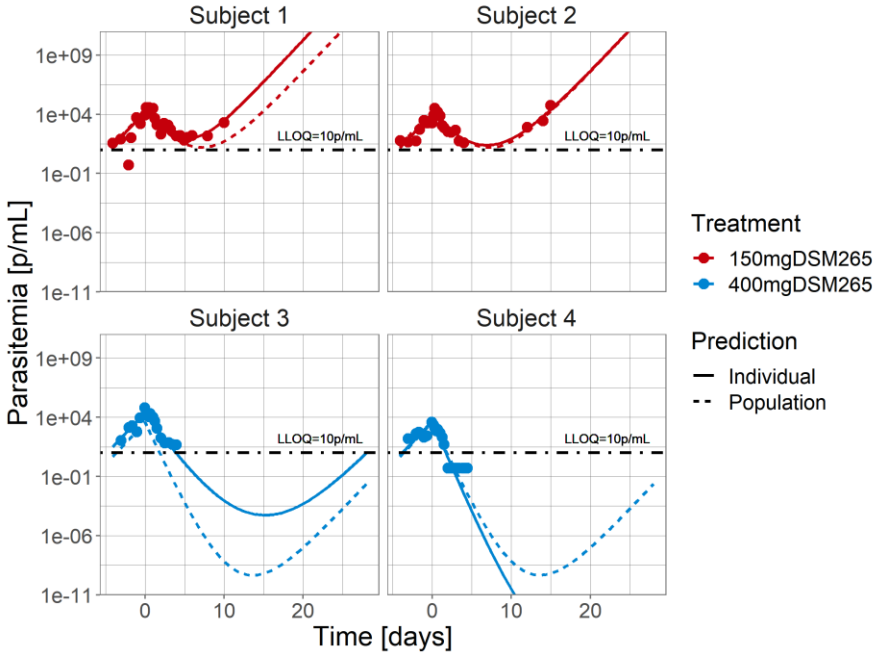
Blood Stage: *PKPD modelling*

⇒ PD parameters estimation

Parameter	Value	RSE
$k_{gr,B}$ (1/hr)	0.068	*FIX*
$E_{max,B}$ (1/hr)	0.186	4.5%
$EC_{50,B}$ (ng/mL)	830	6.6%
γ_B (.)	2	*FIX*
PL_{base} (.)	3.23	8.6%
$\Omega(E_{max,B})$	0.12	23.3%
$\Omega(PL_{base})$	0.94	22.9%
$\beta(E_{max,B}, Dose)$	0.29	29%
$Error_{add}$	1.47	4.9%



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Probability of infection

Direct venous inoculation of *Plasmodium falciparum* sporozoites for controlled human malaria infection: a dose-finding trial in two centres

Benjamin Mordmüller[1*], Christian Supan[1], Kim Lee Sim[2], Gloria P Gómez-Pérez[3], Carmen Lucelly Ospina Salazar[1], Jana Held[1], Stefanie Bolte[1], Meral Esen[1], Serena Tschan[1], Fanny Joanny[1], Carlos Lamsfus Calle[1], Sascha JZ Löhr[1], Albert Lalremruata[1], Anusha Gunasekera[2], Eric R James[2], Peter F Billingsley[2], Adam Richman[2], Sumana Chakravarty[2], Almudena Legarda[3], Jose Muñoz[3], Rosa M Antonijoan[4,5], Maria Rosa Ballester[4,5], Stephen L Hoffman[2†], Pedro L Alonso[3†] and Peter G Kremsner[1†]

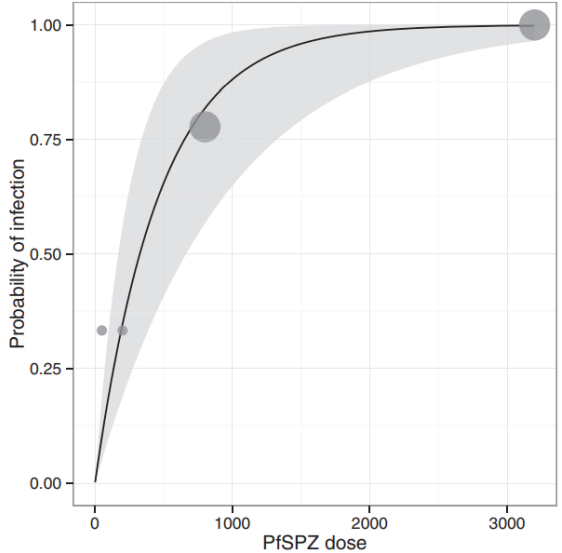

Figure 2 Effect of IV PfSPZ Challenge dose on probability of infection. Observed values are given as grey dots, with size representing weight. Model estimates are represented as the black line and the 95% confidence interval as grey ribbon.

A bit of math:

- p_{spz}: probability of a sporozoite to infect a hepatocyte
- Probability of infection when 800 spz are injected to volunteers is 77%
- Assuming binomial distribution:
  $P(Infection\,|n = 800\,)$
  $= P_{inf} = 1 - \left(1 - p_{spz}\right)^{800}$
- Therefore $p_{spz} = 0.17\%$

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Number of Infected Hepatocytes

Number of injected SPZ:

An estimation of the number of malaria sporozoites ejected by a feeding mosquito

Ronald Rosenberg[1], **Robert A. Wirtz**[1], **Imogene Schneider**[1] and **Robert Burge**[2] *Departments of* [1]*Entomology and* [2]*Biometrics, Walter Reed Army Institute of Research, Washington, DC, USA*

Table. Median values (and ranges) for salivating, infective *Anopheles stephensi*

Values[a]	Lower[b] (n=47)	All (n=93)	Higher[c] (n=46)
Volume	642 (56–1424)	1453 (56–24288)	4795 (1482–24288)
Gland	8740 (100–52109)	8170 (100–105984)	7710 (354–105984)
Eject	8 (0–524)	15 (0–978)	37 (0–978)
Eject/gland	0·001	0·002	0·005
Eject=0	0·17	0·18	0·20

[a]Values tabulated: Volume=number of arbitrary units of saliva expelled; Gland=number of sporozoites in salivary glands; Eject=number of sporozoites ejected; Eject/gland=median number ejected/median number of sporozoites in glands; Eject=0, proportion of mosquitoes ejecting no sporozoites.
[b]Volumes <1453.
[c]Volumes >1453.

Percent of SPZ reaching the liver:

Chronicle of a death foretold: *Plasmodium* liver stage parasites decide on the fate of the host cell

Stefanie Graewe[1], Rebecca R. Stanway[2], Annika Rennenberg[3] & Volker T. Heussler[2]

[1]Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; [2]Institute of Cell Biology, University of Bern, Bern, Switzerland; and [3]Astra GmbH, Hamburg, Germany

The phenomenon of transmigration is discussed in detail below. Surprisingly, only a portion of the injected sporozoites (*c.* 35%) enters a blood vessel and is carried by the bloodstream to the next destination, the liver (Fig. 1). A considerable number (*c.* 15%) ends up not in blood but in lymph vessels, which are a dead end for the parasite. An even bigger portion of sporozoites (*c.* 50%) does not leave the skin tissue at all. Interestingly, it has

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